

Methoxyacetic Acid

CAS #625-45-6

Swiss CD-1 mice, at 0.0, 0.1, 0.2, 0.4% in drinking water

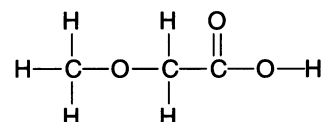
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Methoxyacetic acid, the metabolite of ethylene glycol monomethyl ether, was tested for reproductive toxicity in Swiss CD-1 mice using the RACB protocol (Morrissey et al., *Fundam Appl Toxicol* 13:747-777 [1989]). It was part of a series of glycol ethers and congeners evaluated for structure-activity correlations using this design. Task 1, the dose-range-finding task, was not performed since sufficient information existed in the literature for dose level selection. Concentrations were set at 0.0, 0.1, 0.2, 0.4% in drinking water. These concentrations produced calculated consumption estimates of 0.0, 140, 240, and 390 mg/kg/day.

There were body weight reductions in both sexes during the continuous breeding phase of the study. A 9% reduction occurred in high dose males, while female body weights were reduced by 19% (0.1% dose), 24% (0.2%), and 32% (0.4%). These were related, at least in part, to reductions in water consumption of 19, 30, and 44% in the low, middle, and high dose groups, respectively.

No pairs at the high dose delivered any live young. For the low and middle dose levels, respectively, there was a 14 and 33% reduction in the mean number of litters per pair, and a 33 and 86% reduction in number of live pups per litter, with concomitant increases in the number of dead pups. Additionally, adjusted live pup weight was reduced by 8 and 15%. Thus, there were

significant adverse reproductive effects at the lowest dose.

Because of the reduction in pup number, a crossover mating trial was conducted, using one treated partner from the high dose group and one control partner. A separate group of rerandomized controls served as concurrent controls for this task. Fertility was reduced by 92% for both treated sexes; only one pair in each group bore any young versus 14 of 20 control pairs. Of those single litters, the treated female bore no live young, while the female bred to the treated male bore four live young. Clearly, these numbers are insufficient to perform statistics. Thus, the primary effect was that although all groups showed equal evidence of mating the capability of treated animals to bear live pups was severely reduced.

The controls and high dose mice were killed and necropsied after the end of the crossover mating. In males at the 0.4% dose, testis weight was reduced by 48%, epididymis weight by 32%, and seminal vesicle weight by 18%. Also at this dose, sperm motility was reduced by 75%, sperm number by 89%, and sperm abnormality increased from 6% abnormal (controls) to 92% abnormal (0.4% MAA). Liver and kidney weights were unchanged, and the only histological lesion noted microscopically was testicular atrophy.

The last F₁ litter from the controls and low dose groups in Task 2 was reared by

the dams to weaning, and then dosed with MAA at the same concentration provided to their parents. The treated mice consumed approximately 35% less water than the controls. The high and middle dose F₀ mice had no live young in the fifth litter, and in the low dose group, only 15 males and females survived to weaning. When mated at approximately postnatal day 74, none of the 15 treated pairs had any live young (versus 18 of 20 controls). After delivery of the F₂ litters, the F₁ mice were killed and necropsied. Body weights were reduced by 10% in MAA-treated males and 17% in MAA-treated females. Male liver weight (adjusted for body weight) was increased by 8%, and adjusted female kidney weight was increased by 17%. Epididymal sperm motility was decreased by 40%, epididymal sperm count by 30%, and the percent of abnormal sperm was increased from 7% abnormal in controls to 29% abnormal in this low dose group. The only treatment-related lesion found histologically was scattered testicular atrophy.

Thus, methoxyacetic acid was clearly toxic to the reproductive processes of both sexes when tested at concentrations that produced modest to significant reductions in water consumption. Both sexes were functionally affected at the high dose level (0.4%); the use of a lower dose at crossover would help distinguish the most sensitive sex.

Summary: NTP Reproductive Assessment by Continuous Breeding Study.

NTIS#: PB86164264/AS

Chemical: Methoxyacetic Acid

CAS#: 625-45-6

Mode of exposure: Drinking water

Species/strain: Swiss CD-1 mice

F ₀ generation	Dose concentration →	0.1%	0.2%	0.4%
General toxicity		Male, female	Male, female	Male, female
Body weight		—, ↓	—, ↓	↓, ↓
Kidney weight ^a		•	•	—, —
Liver weight ^a		•	•	—, —
Mortality		—, —	—, —	—, ↑
Feed consumption		•	•	•
Water consumption		↓	↓	↓
Clinical signs		—, —	—, —	—, —

Reproductive toxicity			
̄x litters/pair	↓	↓	↓
# live pups/litter; pup wt./litter	↓, ↓	↓, ↓	•, •
Cumulative days to litter	↑	↑	•
Absolute testis, epididymis weight ^a	•	•	↓, ↓
Sex accessory gland weight ^a (prostate, seminal vesicle)	•	•	—, ↓
Epidid. sperm parameters (#, motility, morphology)	•	•	↓, ↓, ↑
Estrous cycle length	•	•	—

Determination of affected sex (crossover)	Male	Female	Both
Dose level	•	•	0.4%

F ₁ generation	Dose concentration →	0.1%	0.2%	0.4%
General toxicity		Male, female	Male, female	Male, female
Pup growth to weaning		—, ↓	•, •	•, •
Mortality		↑, ↑	↑, ↑	•, •
Adult body weight		↓, ↓	•, •	•, •
Kidney weight ^a		—, ↑	•, •	•, •
Liver weight ^a		↑, —	•, •	•, •
Feed consumption		•	•	•
Water consumption		↓	•	•
Clinical signs		—, —	•	•

Reproductive toxicity			
Fertility index	↓	•	•
# live pups/litter; pup wt./litter	•, •	•, •	•, •
Absolute testis, epididymis weight ^a	↓, ↓	•, •	•, •
Sex accessory gland weight ^a (prostate, seminal vesicle)	—, —	•, •	•, •
Epidid. sperm parameters (#, motility, morphology)	↓, ↓, ↑	•	•
Estrous cycle length	—	•	•

Summary information

Affected sex? Both
 Study confounders: Reduced water consumption
 F₁ more sensitive than F₀? Yes
 Postnatal toxicity: Yes

Legend: —, no change; •, no observation; ↑ or ↓, statistically significant change (p<0.05); —, —, no change in males or females. ^aAdjusted for body weight.